PATENT COOPERATION TREATY

 PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
030077woMe/sto		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/00400	16.01.2003	17.01.2002
International Patent Classification (IPC) or both national classification and IPC		
G01N33/68		
Applicant		
EVOTEC NEUROSCIENCES GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of the demand	Date of completion of this report
12.08.2003	03.05.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Schalich, J Telephone No. +31 70 340-3954

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/00400

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-36 as originally filed

Claims, Numbers

1-32 as originally filed

Drawings, Sheets

1/15-15/15 as originally filed

Sequence listing part of the description, pages:

1-13, filed with the letter of 07-04-2003,

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12,13-17 (partly),20-22,25-29(partly)

   because:

   ☒ the said international application, or the said claims Nos. 12,20-22 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 13-17, 25-29 (partly)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12,16,20-22,25
	No:	Claims	13-15,17-19,23-24,26-32
Inventive step (IS)	Yes:	Claims	4,7
	No:	Claims	1-3,5-6,8-32
Industrial applicability (IA)	Yes:	Claims	1-11, 13-19, 23-32
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 12 and 20-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).
On **claims 12-17 and 25-29** only a limited search has been done and therefore only a limited opinion will be given on the subejct-matter of said claims (see also 4.2).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: KEARNEY J A ET AL: 'A gain-of-function mutation in the sodium channel gene Scn2a results in seizures and behavioral abnormalities.' NEUROSCIENCE. UNITED STATES 2001, vol. 102, no. 2, 2001, pages 307-317

D2: PLANELLS-CASES R ET AL: 'Neuronal death and perinatal lethality in voltage-gated sodium channel alpha(II)-deficient mice.' BIOPHYSICAL JOURNAL. UNITED STATES JUN 2000, vol. 78, no. 6, June 2000 (2000-06), pages 2878-2891

D3: WO 01 38564 A (LAFRENIERE RONALD G ;ROULEAU GUY A (CA); UNIV MCGILL (CA); RAGSDAL) 31 May 2001 (2001-05-31)

D4: US 02004194 A

The document D4 was not cited in the international search report. A copy of the document is appended hereto.

1. Novelty

The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of **claims 13-15, 17-19, and 23-32** is not new for the following

reasons:

1.1. The examination of **claims 13-15 and 17** was restricted to the pharmaceutical use of the SCN2A polynucleotide and polypeptide, antibodies, antisense RNA and known modulators like saxitoxin (see also 4.2.).
Antibodies and antisense RNA are known from D3 (p24, last par to p 25 and p 47, par 2); modulators like saxitoxin from D2 (p 2880, co 2, par 4). It is general knowledge, that the binding of saxitoxin implies the blocking of a sodium channel. Therefore, saxitoxin is clearly a modulator of SCN2a.
Pharmaceutical compositions according to present claims 14 and 15 as well as a kit, according to present claim 17, are described in D3, p 25-26.
Present claims 13-15 and 17, mere product claims, are therefore clearly not novel.
Claim 15, referring to the second medical use of the undefined modulator, is formally novel.
1.2. **Claims 18 and 19** disclose transgenic animals, which express SCN2A as a transgene (claim 18) , for developing diagnostic and therapeutic methods for neurodegenerative diseases or related disorders (claim 19). Claim 18 (i-vi) defines the animal in functional features, whereas (vii) refers to a result to be achieved and does not contain any effective pointer on how to achieve this result.
Document D1 -describing transgenic mice expressing a variant SCN2A, which leads to an altered activity of SCN2A (p310, co 1, par 5 to p311, co 2, par2)- demonstrates massive neurodegeneration (loss of neuronal cells and gliosis) in areas affected by AD, since the dentate gyrus and CA1-3 form part of the hippocampus, which is severely affected in AD (p 312 co 2, par 3 to p 314, co 2, par 2 and fig 7), which leads to premature death (fig. 8). The origin of the neurodegeneration is thereby still unknown (p315, co 2, par 3).
Document D2 -describing SCN2A knock-out mice with a disruption of exon 1- demonstrates that the lack of SCN2A leads to massive neurodegeneration (p 2885, co 2, par 3) and perinatal lethality (p 2885, co 1, par 2).
D2 (p 2890, co 1, last par). The loss of neurons is thereby not due to necrotic changes secondary to hypoxia (p 2885, co 2, last par to p 2886, co 2, par 2). D2 (p 2889, co 1, par 3) even favours the hypothesis, that neurodegeneration in certain parts of the brain induces the hypoxia.
Claims 18 and 19 are therefore not novel.
1.3. **Claims 20-22** disclose screening methods for a modulator of SCN2A based on evaluating the effect of compounds on the level and/ or the activity of SCN2A.

Document D1 (p 2880, co 2, par 4) discloses an assay for binding of saxitoxin, a modulator of SCN2A, to SCN2A, but without intention of finding a modulator for neurodegenerative diseases.
Claims 20 to 21 are therefore novel, implying that also **claim 25** is novel.
1.4. Binding assays for screening of ligands as described by **claims 23 and 24** without the intention to find a modulator of neurodegenerative diseases are described in D3 (p 40, li 16 to p 41, li 7) and are therefore not novel.
1.5. Methods for producing a medicament and medicaments obtained by said methods (present **claims 26-29**) are known from D3, claim 12 and p 25.
1.6. **Claims 30-31** do not refer to a medical use and represent mere product claims. The SCN2A protein per-se is well- known, see D1-3.
1.7. In **claim 32** antibodies are disclosed, which bind SCN2A, and their use in detecting a pathological state of a cell, not further defined. Document D2 discloses SCN2A reactive antibodies (p 2881, co 1, par 2; p 2885, co 2, par 2 and fig 5). Immunocytochemical detection of SCN2A correlates with neuronal apoptosis (p 2885, co 2, par 3) and perinatal lethality (p 2885, co 1, par 2).

2. Inventive Step

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of **claims 1-3, 5-6, 8, 16, 20-22** does not involve an inventive step in the sense of Article 56 EPC.

2.1. Document D4, which is considered as closest prior art, discloses in claim 26 determination of the activity of sodium channels as a method for diagnosing AD. The difference to present claims 1-3 is the lack of specification of a specific sodium cannel (SCN2A). The problem to be solved is therefore the provision of a method of diagnosis of neurodegenerative diseases
In the light of documents D1 and D2 -demonstrating a neurodegenerative effect due to an altered activity (D1) or an altered level of SCN2A (D2)- would the skilled person regard it as obvious to use detection of the activity and/ or levels of SCN2A (gene, protein and fragments thereof) for the diagnosis and monitoring neurodegenerative diseases, especially AD.
Hence no inventive step is present, when determination of the activity or levels of SCN2A is used for diagnosing, monitoring or treatment-evaluation of neurodegenerative diseases, as disclosed in present **claims 1-3.**

Neither does the application of said method in form of a kit (present **claim 11**) or the use of the gene, a translation product of the gene, an antibody, antisense oligonucleotides or known modulators for therapy of neurodegenerative diseases (present **claims 12 and 16**) or the application of assays systems as described by present **claims 20-22** (and consequently **claim 25**), which "per se" form part of the state of the art, to the identification of modulators of neurodegenerative diseases constitute an inventive step.

2.2. Dependent **claims 5-6 and 8-10** do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step, since the presented features are obvious modifications of the methods described in claims 1-3.

2.3. The subject-matter referred to in present **claims 4 and 7** seems to be novel and inventive.

3. Industrial Applicability

Claims 1-11, 13-19, 21-32 are industrially applicable.
For the assessment of the present **claims 12 and 20-22** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Clarity

Claims 1-32 furthermore do not comply with the requirements of Article 6 and Rule 6.3 (a) PCT for the following reasons:
4.1. Although **claims 1-3, 13-15, 25-27 and 28-29** have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack

of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.

Hence, **claims 1-3, 13-15, 25-27 and 28-29** do not meet the requirements of Article 6 PCT.

4.2. Present **claims 12-17 and 25-29** relate to compounds and their use defined by reference to a desirable characteristic or property, namely to modulate a level or an activity of the gene and/or the corresponding protein SCN2A.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for no such products. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved.

Consequently, in the above given examination, an opinion was only given for the following subject-matter:

the pharmaceutical use of the SCN2A polynucleotide and polypeptide, antibodies, antisense RNA and known modulators like saxitoxin.

4.3. The use of the abbreviation SCN2A on its own in **claims 1-32** is ambiguous and unclear.

4.4. The following formulations are relative terms without well-recognized meaning and therefore unclear:

- "reference value representing a known disease or health status" in claims 1-10
- "similar or equal to a reference value representing a known disease status" in claims 11
- "increased risk of developing said neurodegenerative disease" in claim 1
- "increased propensity or predisposition of developing such a disease" in claim 11
- "pathological state" and "altered degree of staining or altered staining pattern ... compared ... known health status"

4.5. The use of the phrases "fragment, derivative or variant" and "variation", the latter not being defined at all, leads to a lack of clarity, particularly in view of the definitions found at pages 5 and 6 of the present application, which merely add to the confusion as to the precise scope of the claims.

4.6. **Claims 1-10, 12 and 25-29** furthermore lack support in terms of technical features with regard to exactly how the diagnosis, prognostication and predisposition or therapy or production of a medicament is actually determined.

4.7. **Claim 11**, directed to a kit for diagnosing a neurodegenerative disease, contradicts Art. 6 PCT, because the feature "an instruction ... or an increased propensity or predisposition of developing such a disease" relates to a method of using the kit rather than clearly defining the kit in terms of technical features. The intended limitations are therefore not clear from this claim.